Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

The rejection of claims 1-44 under 35 U.S.C. § 112 (first paragraph) for lack of enablement is respectfully traversed.

It is the position of the U.S. Patent and Trademark Office ("PTO") (office action, page 3) that although the present application teaches that the compounds of formula (I) exhibit binding selectivity for human α_{2a} and α_{2c} receptors over human α_{2b} receptors, binding affinity data set forth in the application does not demonstrate whether these compounds are agonists or antagonists for α_{2a} and α_{2c} receptors. Applicants respectfully disagree for the following reasons. First, it is a well known fact that yohimbine is a potent α_2-adrenergic receptor antagonist (application page 3, line 10). Likewise, yohimbine dimer compounds of formula (I) possess α_2-adrenergic receptor antagonist activity as demonstrated not only by their binding affinity to α_2-adrenergic receptor subtypes (Table 1), but also by their ability to block medetomidine effects (Table 4). Furthermore, that the yohimbine dimers of the present invention possess α_2-adrenergic receptor antagonist activity is supported by the fact that the yohimbine dimers are prepared by a standard peptide coupling reaction that, due to the conformationally rigid nature of the yohimbine polycyclic ring system, conserves the structural and stereochemical integrity of the yohimbine compounds even after dimerization (application page 20, line 17 to page 21, line 4). In view of the above, persons of skill in the art would recognize that yohimbine dimer compounds of formula (I) function as antagonists of α_{2a} and α_{2c} receptors.

The PTO further asserts that there is no teaching in the specification showing any disease condition which is solely mediated by either an agonist activity or an antagonist activity at specific α_2 receptor subtypes. However, as set forth in the present application at pages 17-19, the α_{2a} and α_{2c} adrenergic receptors have been implicated in numerous diseases. In particular, α_{2a} adrenergic receptors have been implicated in hyper/hypotension, pain, glaucoma, alcohol and drug withdrawal, rheumatoid arthritis, ischemia, migraine, cognitive deficiency, spasticity, diarrhea, and nasal congestion (application page 17, line 11 to page 18, line 10). Furthermore, the α_{2c} adrenergic receptors have been implicated in Raynaud's disease (application page 18, line 11 to page 19, line 28).

The PTO is also of the position that the compounds of formula (I) encompass hundreds of thousands of compounds and it would therefore require undue experimentation to demonstrate the efficacy of instant compounds in known animal models. Applicants respectfully disagree. As noted above, the examples of the present invention demonstrate that a number of the claimed dimers exhibit enhanced selectivity as antagonists of the α_{2a} or α_{2c} adrenergic receptors. For this reason, persons of skill in the art would fully appreciate that other dimer compounds within the scope of the present invention will likewise exhibit improved selectivity and, thus, afford treatment of α_{2a}– or α_{2c}– mediated conditions or disorders.

For all of the above reasons, the rejection of claims 1-44 under 35 U.S.C. § 112 (first paragraph) for lack of enablement is improper and should be withdrawn.

The rejection of claims 1-44 under 35 U.S.C. § 112 (second paragraph) for indefiniteness is respectfully traversed in view of the above amendments. The rejection should therefore be withdrawn.

The rejection of claims 1-44 under 35 U.S.C. § 103(a) for obviousness over Zheng et al., "Yohimbine Dimers Exhibiting Binding Selectivities for Human α_{2a}–versus α_{2b}–Adrenergic Receptors," *Bioorganic & Medicinal Chemistry Letters* 10:627-630 (2000) ("Zheng") is respectfully traversed.

The attached Declaration of Duane D. Miller under 37 C.F.R. § 1.132 ("Miller Declaration") demonstrates that Zheng is not prior art, because Zheng does not evidence knowledge or use of the claimed invention by others in this country prior to the invention by the applicants of the above-identified application. Specifically, Dr. Miller has declared that "the claimed invention of the above-identified application was conceived by me and...co-inventors [Weiping Zheng, Robert Moore, Jr., Suni Mustafa, Dennis R. Feller, Longping Lei, and Shilpa Lalchandani]" (Miller Declaration, ¶¶ 3, 5). Dr. Miller has further declared that coauthor Guoping Sun did not contribute to the conception of the invention as described and now claimed in the present application (see Miller Declaration, ¶ 6). Thus, in view of the Miller Declaration, Zheng is not available as prior art. *See In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982).

Therefore, the rejection of claims 1-44 under 35 U.S.C. § 103(a) for obviousness over Zheng is improper and should be withdrawn.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: January 31, 2005

Edwin V. Merkel
Registration No. 40,087

NIXON PEABODY LLP
Clinton Square, P.O. Box 31051
Rochester, New York 14603-1051
Telephone: (585) 263-1128
Facsimile: (585) 263-1600

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450, on the date below.

1/31/05 | Wendy L. Barry
Date